Principal Conclusions

The science base for assessing tobacco harm reduction is incomplete. Nonetheless, the presence of potential reduced-exposure products (PREPs) on the market suggests an urgent need for proactive plans to evaluate the potential risks and benefits. The potential for reduction in morbidity and mortality that could result from the use of less toxic products by those who do not stop using tobacco justifies inclusion of harm reduction as a component in a broad program of tobacco control. To date there are two general types of PREPs: pharmaceuticals and modified tobacco products. The pharmaceuticals include, for example, nicotine replacement therapy (NRT) and bupropion, while modified tobacco products include products with modified tobacco and those with modified delivery systems.

Having identified conceptual and operating precepts as stated at the end of Chapter 1, the committee concludes that there can be a successful, scientifically-based harm reduction program that is justifiable and feasible – but only if implemented carefully and effectively and only if:

- Manufacturers have the necessary incentive to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease;
- Consumers are fully and accurately *informed* of all of the known, unknown, likely, and potential consequences of using these products;
- Promotion, advertising and labeling of these products are firmly *regulated* to pre-vent false or misleading claims, explicit or implicit;
- Health effects of using PREPs are *monitored* on a continuing basis;
- Basic, clinical, and epidemiological *research* is conducted to establish the potential use of PREPs for reducing risks for disease in individuals and for reducing harm to the population as a whole, and,
- Harm reduction is implemented as a component of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

The 7 chapters of the committee's report that precede this and the extensive reviews found in Section II provide the documentation for the following principal conclusions regarding the four questions posed within the charge, as outlined in Chapter 1. Specific recommendations can be found within the body of the report.

Conclusion 1. *For many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible.* This conclusion is based on studies demonstrating that for many diseases, reducing tobacco smoke exposure can result in decreased disease incidence with complete abstinence providing the greatest benefit. Key to this conclusion is the

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assumption that compensatory increase in exposure does NOT occur with the use of these products.

Conclusion 2. *PREPs have not yet been evaluated comprehensively enough (including for a sufficient time) to provide a scientific basis for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use.* (One exception is the use of nicotine replacement therapy for maintenance of cessation in the Lung Health Study. See Chapters 13 and 14.) Carefully and appropriately conducted clinical and epidemiological studies could demonstrate an effect on health. However, the impact of PREPs on the incidence of most tobacco-related diseases will not be directly or conclusively demonstrated for many years. Tobacco use causes very serious morbidity and mortality due to several different diseases. Cancer (e.g. of the lung, oral cavity, esophagus, and bladder), cardiovascular disease, chronic obstructive pulmonary disease, and low birthweight are all well-established effects of tobacco use. The conditions can be diagnosed, the natural history of the diseases is reasonably well understood, and scientifically appropriate studies of tobacco users who switch to PREPs could be designed. See Chapters 4 and 11-16 for supporting material.

However, such research will be difficult. For example, tobacco users may not use a particular PREP for long enough to see health impact; tobacco PREPs will undoubtedly change substantially over the next decade; many subjects would be required for adequate statistical power. For all these and other reasons, conclusive proof of the health effects of PREPs will not be available in the near future, as new PREPs are entering the marketplace. Thus, for purposes of educating the public about PREPs and for purposes of regulating health claims, surrogate measures of health effects must be considered.

Conclusion 3. *Surrogate biological markers that are associated with tobacco-related diseases could be used to offer guidance as to whether or not PREPs are likely to be risk-reducing.*. However, these markers must be validated as robust predictors of disease occurrence, and should be able to predict the range of important and common conditions associated with conventional tobacco products in order to be useful for PREP evaluation and regulation. PREPs may differentially affect risk of tobacco-related diseases. Furthermore, the efficacy of PREPs will likely depend on user population characteristics, e.g. those defined by gender, genetic susceptibility, ethnicity, tobacco history, and medical history. Chapters 12 - 16 describe clinical studies using surrogate indicators that could be conducted to better understand whether or not PREPs would decrease specific adverse health outcomes. The potential studies vary in terms of the length of time that would be required to document the effect, the number of patients, and the power of the study to predict disease outcome. There is no one panel or group of tests that the committee could recommend at this time that would, as a whole, serve to assure that morbidity and mortality would decrease with use of PREPs.

Conclusion 4. *Currently available PREPs have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.* There are many techniques to assess exposure reduction, but the report contains many caveats about the use of all of them, including usually an unknown predictive power for harm. Long-term use of pharmaceutical preparations for maintenance of tobacco cessation will clearly achieve exposure-reduction. The safety of these products for long-term use, however, is not well established. For example, it is well known that nicotine affects the autonomic nervous system, with uncertain long-term con-

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sequences. However, even if NRT use for maintenance of cessation results in nicotine exposure equivalent to that achieved with conventional tobacco products, exposure to the most harmful tobacco toxicants is avoided. See Chapters 4, 9, and 11 for supporting material.

There is insufficient evidence to decide whether concomitant use of NRT or bupropion with decreased tobacco use will lead to significantly decreased exposure to tobacco toxicants such as tar and carbon monoxide. Nor is there sufficient evidence to determine how much this PREP strategy will decrease conventional tobacco use or how much compensation will occur. However, there are exposure assessment tools to assess this issue, as described in Chapter 7.

Tobacco-related PREPs pose different exposure assessment problems. PREPs characterized by the reduction (or, conceivably, elimination) of one class of toxicants, such the reduced-nitrosamine preparations in varying stages of development and marketing, do result in decreased exposure per cigarette to specific toxicants. Analytic techniques exist to demonstrate this. However, the smoking behavior of people who use these PREPs has not been researched well enough to know whether or not compensation occurs (thus increasing net exposure to other toxicants and possibly maintaining exposure to the potentially reduced chemical). Furthermore, there are insufficient data to allow scientific judgement or prediction of the health effects of removal of one class of chemicals from tobacco products.

The cigarette-like PREPs that use heat or reduced burn temperature of tobacco and deliver aerosolized nicotine pose other exposure assessment problems. The prototypes available now have only just begun to be studied by researchers other than the manufacturers. It is clear that the yield of some of these products is different from that of conventional cigarettes. The pattern of yield changes suggests differential reduction in exposure to toxicants. Some preliminary data suggest increased yield of specific toxicants concomitant with no change or decreases in others.

There does not exist a standard reference product for comparison with tobacco-related PREPs. Assessment of the risk from use of a PREP requires comparison to the risk of the product avoided AND to the risk of the product (including no product, or abstinence) the PREP user would switch to if the PREP were NOT available.

Conclusion 5. *Regulation of all tobacco products, including conventional ones as recommended in IOM, 1994, as well as all other PREPs is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected.* Regulation is needed to assure that adequate research (on everything from smoke chemistry and toxicology to long-term epidemiology) is conducted and to assure that the public has current, reliable information as to the risks and benefits of PREPs. Careful regulation of claims is needed to reduce misperception and misuse of the products. If a PREP is marketed with a claim that it reduces (or could reduce) the risk of a specific disease(s) compared to the risk of the product for which it substitutes, regulation is needed to assure that the claim is supported by scientifically sound evidence and that pertinent epidemiological data is collected to verify that claim. The regulation proposed by this committee is narrowly focused on assuring that the products reduce risk of disease to the user and accumulating data that would indicate whether or not the products are harm-reducing for the population in the aggregate. Other potential regulatory approaches to tobacco control are not addressed within this report. See Chapter 7 for supporting and explanatory material.

Conclusion 6. *The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.* The effect on public

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health will depend upon the biological harm caused by these products and the individual and community behaviors with respect to their use. Assessing the public health impact will be difficult and will require classic public health tools of surveillance, research, education, and regulation to assure that the impact is positive. The major concern for public health is that tobacco users who might otherwise quit will use PREPs instead, or others may initiate smoking, feeling that PREPs are safe. That will lead to less harm reduction for a population (as well as less risk reduction for that individual) than would occur without the PREP, and possibly to an adverse effect on the population. PREPs should be a last resort only for people who absolutely can not or will not quit. Population-based research and surveillance can determine whether the intended impact is achieved. However, measurements of health impact at the population level can take years to document, as described in previous sections of this chapter and in the report as a whole.

Regulation of PREPs can only assure that a specific PREP could be risk-reducing for a person who uses it compared to the conventional product it replaces. Regulation cannot assure that the availability of risk-reducing PREPs will lead to reduced tobacco-related disease in the population as a whole. However, a regulatory agency can assure that data are gathered that would permit the population effects to be monitored. If population tobacco product use increases or tobacco-related disease increases, these data would serve as a basis for developing and implementing appropriate public health interventions. See Chapters 3, 6, and 7 for supporting material.

Studies using surrogate indictors of population impact could be designed. For example, monitoring the perception that the public, particularly tobacco users and adolescents, has of the risks and benefits of PREPs is possible. Research indicating that people perceive PREPs to be more beneficial than scientific judgment indicates would provide early evidence of the risk for an adverse public health impact. Action of various sorts (e.g. regulatory review of claims, public health education campaigns) could then be taken.

Chapters 1 and 5 include discussions of the utility of a risk assessment framework for organizing the scientific basis for evaluation of PREPs. It is useful to return to that framework to put the committee's conclusions and recommendations into the proper light. Although the committee did not perform a risk assessment for any existing PREP, the committee's conclusions and recommendations provide a means to assure that a risk assessment can be done in the future. As Table 8-1 illustrates, the Committee's principal conclusions (discussed in a preceding section of this chapter) assume use of the conventional risk assessment framework, and the conclusions and recommendations for surveillance and regulation point a way to develop the necessary data for such an evaluation.

Hazard identification is inherent in the first question of the committee's charge, Does the product decrease exposure to the *harmful substances* in tobacco? The principal conclusions that harm reduction is feasible and that exposure reduction can be demonstrated require identification of the toxicants within or produced by use of the PREP. The element of the proposed surveillance system related to specific tobacco constituents and several of the regulatory principles (#1, #3, #7, #8, #9) will assure that the necessary toxicology data are gathered, validated, and made available to scientists, public health officials, and regulators.

Dose-response assessment is inherent in the second question of the charge, Is decreased exposure associated with decreased harm to health? An important issue when considering this question in the context of PREP assessment is that while some data are available when assessing a dose-response relationship, there are virtually no data describing the change in response due to dose reduction after a period of higher exposure. This data would reflect the extent of disease

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reversibility or halting of disease progression possible from exposure reduction. Dose–response assessment is also inherent in the third question of the charge, Are there useful surrogate indicators of disease that could be used? The principal conclusion that surrogate measures could be used to predict harm reduction requires the development of surrogate disease indicators (response) so that a dose-response assessment (and therefore a risk characterization) could be made in some reasonable timeframe, without waiting decades to assess cancer morbidity and mortality. The surveillance system component addressing disease outcomes will help provide some of these necessary data and the regulatory principle #6 requiring post-marketing surveillance and epidemiologic studies for PREPs with claims will assure that the data are collected.

Exposure assessment is inherent also in the first question of the committee's charge. The principal conclusion that exposure reduction can be demonstrated is fairly straightforward. Several components of the proposed surveillance system will provide important exposure information and at least 4 regulatory principles (#2, #4, #9, #11) would assure that relevant data are collected.

Risk characterization is the central question of the report and, indeed, of harm reduction writ large. The fourth question of the committee's charge regarding the public health impact of the products is perhaps the most important asked of the committee. The principal conclusions that harm reduction is feasible but not yet convincingly demonstrated and that a beneficial public health impact is not assured are two that are most easily misunderstood as contradictory if not carefully considered. They drive important considerations of the report – harm reduction should be pursued and encouraged but every aspect of it should be watched and studied vigilantly. Appropriate tools of public health must be available and must be powerful. Surveillance of personal tobacco product use and related behavioral patterns and of disease outcomes will provide some of the data necessary to assure a positive population impact. The regulatory principle that labeling for PREPs with claims cannot be false or misleading is another necessary safeguard against a negative public health impact.

Risk management, the culmination of the risk assessment process, is directly related to the committee's principal conclusion that regulation is a necessary precondition for advancing knowledge and for ensuring a public health benefit. Two of the most important tools for a risk manager, are knowledge, which will be developed if the research and surveillance recommendations are followed and if the regulatory principles #1-9 are adhered to, and enforcement power, which is called for in regulatory principle #10. A properly conducted risk assessment outlines gaps in the knowledge required by the risk manager and the assumptions used for the risk characterization in the absence of complete data. Explicit description of these assumptions can help identify the research that will most significantly improve understanding of risk and, thereby, affect public policy.

Questions asked by a risk manager help to integrate the scientific data and assumptions provided by the formal risk assessment into the desired public policy. The questions also assure that regulation, a risk-management tool for tobacco harm reduction proposed by this committee, is based on and informed by the risk assessment process. Questions might include:

- Which of the thousand known tobacco-related toxicants are most important to consider in the assessment of risk? Is the scientific data available for adequate hazard identification?
- Are the data presented by the manufacturer based on assays reflecting the manner in which the product is actually used by the consumer?
- Are the claims by the manufacturer adequately supported by the scientific data? Is the risk characterization accurately conveyed in a manner understandable to the consumer?

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- What constitutes a substantial degree of overall risk reduction?
- Who has the burden of proof for each type of claim? Is the burden of proof sufficient to assure the products will provide a benefit to the user? Is the burden of proof so high that innovation will be stifled and the possible benefit never realized?
- What can be done immediately to manage the possible risks of these products, given that the science base is currently inadequate?
- Are there parties responsible for assessing and assuring harm reduction outside this regulatory agency? And if so, are the boundaries of risk-management responsibility and authority clear to all parties?

The data presented and scientific limitations identified in Chapter 5, the surveillance system outlined in Chapter 6, and the regulatory framework described in Chapter 7 provide a sound basis for the risk management for tobacco harm reduction.

In summary, tobacco harm reduction could lead to reduced risk of disease for those who cannot give up tobacco. Unfortunately, without the appropriate public health tools of research, surveillance, education, and regulation, tobacco harm reduction could result in a personal and public health disappointment.

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Table 8-1 Relationship of Conclusions and Recommendations for PREP Risk Assessment

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
Committee Charge	1. Does product decrease exposure to the **harmful substances** in or produced during use of tobacco?	2. Is decreased exposure associated with decreased harm to health? 3. Are there useful surrogate indicators of disease that could be used?	1. Does product decrease exposure?	4. What are the public health implications?	4. What are the public health implications?
Principal Conclusions	1. Risk reduction is feasible 4. Exposure reduction can be demonstrated.	3. Surrogate measures could be used to predict risk reduction	4. Exposure reduction can be demonstrated	1. Risk reduction is feasible 2. Risk reduction not yet demonstrated 6. Public health impact is unknown	5. Regulation is a necessary precondtion for asuring a science base and for assuring protection of the health of the public
Elements of surveillance system	Specific tobacco constituents of both the products and the smoke they generate	Disease outcomes	Consumption of tobacco products and of PREPs Biomarkers of exposure to tobacco products Personal tobacco product use and related behavioral patterns	Disease outcomes	Tobacco product marketing, including PREPs
Regulatory Principle **(all refer to tobacco-related PREPS, except for 11)**	1. Ingredient disclosure 3. Preclinical testing required to support health-related claims 7. Evidence for no increased risk 8. Added ingredient review 9. Performance Standards	6. Products with claims would require post-marketing surveillance and epidemiological studies	2. Yield Assessment 4. With specific claims, no increased exposure to unclaimed compounds 9. Performance Standards 11. Exposure reduction claims for pharmaceutical PREPs	5.Labeling for products with claims cannot be false or misleading	10. Enforcement power
Research and other Recommendation	3. Develop appropriate animal models and in vitro assays of pathogenesis	1. Sufficient data to allow estimation of D-R 2. Develop validated biomarkers of disease	4. Clinical and epidemiological studies in human are required	Comprehensive surveillance is recommended	Regulation is recommended

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